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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,702	06/01/2001	Eugen Koren	11669.72USU1	9131

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EXAMINER
SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/05/2002

16

Please find below and/or attached an Office communication concerning this application or proceeding.

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 7/16/02

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-34 is/are pending in the application.
Of the above, claim(s) 14-19, 21-29, 32-34 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-13, 20, 30, 31 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-34 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7-10, 12
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION--

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election with traverse of Invention I, with an election of species of Thrombopoietin in Paper No. 14 is acknowledged. The traversal is on the ground(s) that the examination of the entire application would not constitute a burden to search. This is not found persuasive because contrary to applicants' assertion that any search of the prior art in regard to group I will reveal whether any prior art exists as to the other Groups, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter.

The requirement is still deemed proper and is therefore made FINAL.

Applicants requested clarification of the groupings: Claims 30 and 31 are properly grouped with Invention I. The Examiner regrets the error.

Claims 1-13, 22, 30 and 31 are under consideration.

Objections and Rejections under 35 U.S.C. §112:

Claim 31 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Transforming a host cell does not further limit a method of modifying a nucleic acid.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13, 22, 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are confusing, and therefore indefinite because of the inconsistent use of the terms "human" and "animal". Claim 1 would seem to consider humans not to be animals, claims 2-3 would seem to exclude humans (which may not be applicants intent), and claim 5 indicates that humans *are* animals. Because of these inconsistencies, the claims are indefinite.

In claim 10, it is not clear how the immunodominant epitope is identified by binding to antibodies from both naive and non-naive individuals. Such is unclear as a method step, as it is not clear in what order the two things are done, nor how the result identifies the immunodominant epitope. Further, it would seem apparent that if a naive individual has an antibody to a particular protein, that non-naive individuals would have that same antibody. While it is understood that the epitope must bind both to an antibody from a naive and one from a non-naive subject, it is not clear to the Examiner that there would exist any epitopes that meet the former but not the latter requirement, which raises the question of whether the naive and non-naive individuals are from the same or different species- this issue applies also to other claims, such as claims 11 and 22.

In claim 12, the significance of the recitation that the antibody does not substantially inhibit a therapeutic activity of the therapeutic peptide is unclear; any antibody that binds to the peptide would reasonably be expected to inhibit at least one activity, e.g. inhibit clearance, or increase clearance and therefore inhibit serum half-life. Accordingly, it is not seen how an antibody could meet the limitation of the claim, nor how that limitation relates to part (b) of the claim.

Claim 13 is indefinite because by using the definite article "the", it implies that there will be only a single immunodominant epitope that is not located in a region of the polypeptide, which may or may not be the case. Amendment of part (b) to read *"an* immunodominant epitope" would be remedial.

Claim 22 is incomplete, as there are no method steps that would accomplish the goal of part (b); it is not clear how one determines "whether the identified epitope is in at least one immunodominant epitope in the polypeptide."

Claim 30 is incomplete for failing to state how an immune response is 'reduced'; from reading the specification, it would appear that what is actually intended is that the epitope is modified to reduce or eliminate binding of the antibody used to identify it, none of which is reflected in the claim.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8-13, 22, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/10755 (Lovborg et al.), cited by applicants, in view of WO99/53038 (Estell et al.), cited by applicants.

Lovborg et al. disclose a method of mapping immunodominant epitopes of desired proteins, and then producing less immunogenic variants of such proteins by recombinant DNA methods; see abstract and claims, especially claims 1, 5, 6, 18 and 19. Preferred proteins to be mutated include "medicinal proteins, e.g. hormones, e.g. insulin, HCG, or growth hormone, or medicinal enzymes...",

and "interleukins, or interferons, are of special interest." See page 5. The epitope mapping is performed using antibodies, see pages 6-7. They state that the epitopes in the protein are changed by genetic engineering or chemical modification through 'well established techniques' see page 6. Exemplified species were made via substitution or deletion of residues, see page 10. Human proteins are preferred species, see page 2.

The disclosure of Lovborg et al. differs from the claims in that it does not teach or suggest using antibodies from naive individuals.

Estell et al. teach a method of identifying immunodominant epitopes using T cells from naive human individuals, see page 4-5, for the purpose of preventing an initial reaction to a protein.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Lovborg et al. to use antibodies from naive individuals in view of the disclosure by Estell et al. that mapping epitopes using materials from naive individuals can be useful in preventing initial reactions to therapeutic proteins. Accordingly, it would have been obvious to use antibodies from naive individuals to prevent such initial reactions, as well as from dosed individuals, for the purpose of preventing subsequent reactions. The person of ordinary skill in the art would appreciate that it is the net result that would be of importance, and the order in which the steps were performed (naive vs. dosed) would not be of significance. It is noted that virtually any protein would meet the limitation claim 2, in that it would be 'homologous', at some level, to part of a native sequence, and of claim 3, in that it would be identical to a part of a native sequence (e.g. 2 amino acid residues) of an endogenous peptide in the animal. With respect to claim 12, see rejection under 35 U.S.C. § 112, second paragraph, above. With respect to claim 13, it would further be obvious *not* to alter epitopes that would destroy the therapeutic activity of the desired protein. Thus, the invention, taken as a whole, is prima facie obvious over the prior art.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/10755 (Lovborg et al.), cited by applicants, in view of WO99/53038 (Estell et al.), cited by applicants as

applied to claims 1-6, 8-11, 22, 30 and 31, above, and further in view of Garrity et al., U.S. Patent Number 5,585,250.

Claim 7 adds the limitation that the protein is mutated by introduction of glycosylation or pegylation.

Garrity et al. teach "immunodampening", or the 'hiding' of epitopes, by adding N-glycosylation sites to a desired protein, see columns 4 and 6.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to further modify the methods and proteins rendered obvious over Lovborg et al. and Estell et al., above, by adding N-glycosylation sites as taught by Garrity et al., for the disclosed purpose of immunodampening the resultant proteins.

Claim 1-11, 22, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/10755 (Lovborg et al.), cited by applicants, in view of WO99/53038 (Estell et al.), cited by applicants, in view of Bartley et al., U.S. Patent Number 5,795,569, cited by applicants, and in the case of claim 7 further in view of Garrity et al., U.S. Patent Number 5,585,250.

This additional rejection is made to address the elected species, thrombopoietin. The teachings and findings of obviousness with respect to growth hormones and cytokines generically, are given above. Bartley et al. teach that it is desirable to decrease the immunogenicity of TPO, referred to therein as MGDF. See column 5 lines 21. Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to apply the methods found obvious above to thrombopoietin or MGDF, as taught by Bartley et al.

Advisory Information:

No claim is allowed.

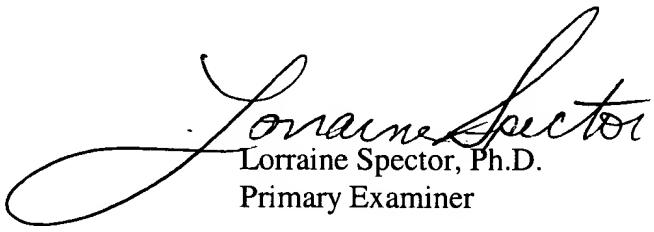
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.



Lorraine Spector, Ph.D.
Primary Examiner

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